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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/781,060	02/17/2004	Spyridon Artavanis-Tsakonas	7326-131	8375

20583 7590 05/06/2011

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EXAMINER	
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ART UNIT	PAPER NUMBER
1649	

MAIL DATE	DELIVERY MODE
05/06/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/781,060	ARTAVANIS-TSAKONAS ET AL.	
	Examiner	Art Unit	
	Kimberly A. Ballard	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34,91-94,96-106,108-111 and 113-116* is/are pending in the application.

4a) Of the above claim(s) *101-106,108-111,113,114 and 116* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34,91-94,96-100 and 115* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/21/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 21, 2009 has been entered.

Status of Application, Amendments, and/or Claims

2. Claims 34 and 105 have been amended as requested in the response filed December 21, 2009. Following the amendment, claims 34, 91-94, 96-106, 108-111 and 113-116 are pending in the current application.

3. Claims 101-106, 108-111, 113, 114 and 116 have been withdrawn from consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected species, there being no allowable generic or linking claim.

4. Accordingly, claims **34, 91-94, 96-100** and **115** are under examination in the current office action.

5. The indicated allowability of claims 96-100 is withdrawn in upon further consideration of the evidence of record, including several of the references cited by Applicant in the response filed December 21, 2009, which will be discussed further below.

Information Disclosure Statement

6. The information disclosure statement (IDS) submitted December 21, 2009 has been considered and the references therein are of record.

Maintained and New Claim Rejections

Claim Rejections - 35 USC § 112, first paragraph

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 34, 91-94, 96-100 and 115 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is maintained for reasons of record and is further reinstated for claims 96-100 upon further consideration as discussed below.

The claims, as amended, are drawn to a method of treating a disease or disorder in a human in which the disease or disorder is a malignancy characterized by increased Notch activity or increased expression of a human Notch protein or of a Notch derivative capable of being bound by an antibody to a human Notch protein, relative to said Notch activity or expression in an analogous non-malignant sample, comprising administering to a human in need of such treatment a therapeutically effective amount of a molecule which antagonizes the function of a human Notch protein, wherein the molecule is (i) a protein capable of inhibiting the interaction of said Notch protein with another toporythmic protein, or (ii) an antibody to said human Notch protein or a portion of said antibody containing the idiotype thereof, or (iii) an oligonucleotide which (a) consists of at least six nucleotides, (b) consists of at least a sequence complementary to at least a portion of a RNA transcript of a toporythmic gene; and (c) is hybridizable to the RNA transcript. Hence, the claimed therapeutic method still encompasses the treatment of a broad spectrum of diseases and disorders comprising the use of a genus of protein, antibody and oligonucleotide molecules defined functionally but not structurally.

Response to Arguments

9. At pp. 5-7 of the response filed December 21, 2009, Applicants argue that claim 34 as amended now recites an antagonist molecule as one that directly inhibits the Notch pathway either as a protein capable of inhibiting the interaction of a human Notch protein with another toporythmic protein (e.g., an antibody to a Notch, Delta or Serrate protein or a competitive inhibitor of such binding), or as an oligonucleotide

complementary to at least a portion of a toporythmic gene (e.g., a Notch, Delta or Serrate gene). Applicants submit that a protein capable of inhibiting the interaction of Notch protein with another toporythmic protein is fully described. According to Applicants, human Notch and a representative number of other toporythmic proteins were known and characterized at the time the invention was made, including Delta, Serrate, Mastermind, Suppressor of Hairless and Hairless.

Applicants' arguments have been considered but are not persuasive. In particular, in view of the specification's definition of "toporythmic genes", the claims are not limited to Notch, Delta, Serrate or any of the other genes listed above but broadly encompass any gene or gene product *yet to be identified* as interacting with any of Notch, Delta or Serrate. This would include known and unknown proteins and other molecules. Accordingly, the skilled artisan would not be able to identify antagonists of Notch/toporythmic protein interactions – be they proteins, antibodies, or complementary oligonucleotides – of these yet to be identified toporythmic proteins. At the very least, the identity of the protein would have to be known to even begin screening for appropriate antagonists, and the structure of the gene or gene product would have to be known to develop appropriate oligonucleotide molecules that are complementary to at least a portion of the RNA transcript of the gene. The specification does not provide sufficient structural information for the breadth of such unidentified toporythmic proteins, nor is such guidance available in the prior art. Further, no guidance is provided on the structure of antagonist molecules (such as antibodies or oligonucleotides) directed to Mastermind, Hairless, or Suppressor of Hairless genes/proteins, nor a structure/function

correlation for which region of these genes or their encoded proteins should be used or targeted for antagonism of Notch function. While the prior art references noted by Applicants may teach the sequences of these genes, they are silent with respect to which portions of the encoded proteins are necessary or sufficient for Notch interaction.

Moreover, even if the claims were limited to protein fragments of Notch, Delta or Serrate only, antibodies to these proteins, or oligonucleotides complementary to a portion of these genes, there is nothing to limit the structure of the claimed molecules. For example, the protein that inhibits Notch interactions is not limited to antibody molecules as Applicant implies, but encompasses any peptide or polypeptide within the protein class that meets the functional limitations of the claim. Such a protein molecule includes not only proteins that directly bind to and inhibit Notch itself, but also protein molecules which indirectly antagonize Notch function by blocking or inhibiting Notch ligands, Notch downstream signaling molecules, or other toporythmic proteins such as Delta or Serrate. Only one protein is specifically described in the specification as potentially useful as a therapeutic molecule: a protein consisting of EGF-like repeats 11 and 12 of Notch. This lone species does not support the genus of protein molecules presently claimed. Similarly, only one oligonucleotide molecule is specifically described: an oligonucleotide comprising a sequence antisense to the sequence encoding ELR 11 and ELR 12 of human Notch (see p. 33, lines 20-24). Again, this single species does not support the full genus of oligonucleotide molecules presently claimed. There is insufficient guidance provided in the present specification to demonstrate that Applicants were in possession of this (arguably still broad) genus of molecules. Apart

from molecules which bind to or interact with the EGF-like repeats 11 and 12 of Notch protein, there is little other guidance as to which portions of Notch or of the other toporythmic proteins could be used as antagonist molecules or else are appropriate targets for antagonist molecules.

With respect to antibodies that specifically bind to human Notch protein or antibodies containing the idiotype thereof, the Examiner concedes that generically, such antibodies are described by the specification in view of the disclosed sequence for human Notch. However, the claims recite that the antibody must also be a molecule which antagonizes the function of Notch protein, such as a neutralizing antibody, consistent with the therapeutic intent of the method. No such neutralizing antibodies are demonstrated by the instant specification, nor would the skilled artisan be able to readily distinguish such neutralizing antibodies from the genus of anti-Notch antibodies encompassed by the claims. The specification teaches only that antibodies directed to the extracellular domain of Notch, and in particular ELR 11 and ELR 12 of Notch, are potentially useful as therapeutics. However, claims are not limited to a specific epitope of Notch. The relevant art indicates that even when antibodies are directed to the extracellular ligand-binding portion of Notch, they are not necessarily Notch antagonists but may actually function as Notch *agonists* (see Conboy et al. *Science*, 2003; 302:1575-1577; discussed below as well).

Therefore, the recitation of a molecule which antagonizes the function of a human Notch protein, wherein the molecule is an inhibitory protein, anti-Notch antibody, or an oligonucleotide complementary to a portion of a toporythmic gene, does not meet

the written description provision of 35 U.S.C. 112, first paragraph, because there is insufficient guidance and direction of the claimed molecule as broadly encompassed by the present invention.

At p. 7-8 of the response, Applicants argue that an antibody to a toporythmic protein meets the written description requirements of Section 112 since the toporythmic proteins are uniquely identified and distinguished from other proteins. Applicants also assert that the amino acid sequences within Notch, Delta and Serrate that are required for protein-protein interaction with other toporythmic proteins are provided at Sections 7-8 on pages 67-77 of the specification.

Applicants' arguments have been considered but are not persuasive. As discussed above, the claimed antagonist molecules are not limited to antibodies directed to toporythmic proteins, and even if they were, the claimed invention encompasses such protein yet to be identified which would not, of course, have any structural information available. Further, Sections 7-8 only provide disclosure on Notch-Delta or Notch-Serrate interactions, which is far more constrained than the breadth of the claims which includes Notch interaction with *any* other toporythmic protein. Detailed information pertaining to the structure or structure/function correlation of other toporythmic proteins (besides Delta and Serrate) that interact with Notch is absent from the present specification. Distinguishing structural characteristics that could help to identify members of the claimed genus of proteins, antibodies, or oligonucleotides from others in their respective classes are lacking from the instant specification. The skilled artisan would thus not have recognized that Applicants were in possession of the vast

repertoire of antagonist molecules encompassed by the claimed invention. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus nor guidance as to which of myriad of molecules that are encompassed by the claimed Notch antagonists would be effective in the treatment of malignancy characterized by increased Notch activity or expression in a subject.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

The skilled artisan cannot envision the detailed chemical structure of the encompassed Notch antagonists, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of identification and isolation of such antagonists. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Therefore, the full breadth of the claims does not meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath*

makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

10. Claims 34, 91-94, 96-100 and 115 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Upon further consideration of the evidence of record, this enablement rejection has been recast and now encompasses claims 96-100. Applicant's arguments pertinent to the present rejection will be addressed below.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. *In re Wands*, 8 USPQ2d, 1400 (CAFC 1988).

Breadth of the Claims

As amended, the claims are drawn to a method of treating a human having disease or disorder which is a malignancy characterized by increased Notch activity or increased expression of a human Notch protein or of a Notch derivative capable of being bound by an antibody to a human Notch protein, relative to said Notch activity or expression in an analogous non-malignant sample, comprising administering to a

human in need thereof a therapeutically effective amount of a molecule which antagonizes the function of a human Notch protein, wherein said molecule is (i) a protein capable of inhibiting the interaction of said human Notch protein with another toporythmic protein, or (ii) an antibody to said human Notch protein or a portion of said antibody containing the idiotype thereof, or (iii) an oligonucleotide which (a) consists of at least six nucleotides, (b) consists of a least a sequence complementary to at least a portion of a RNA transcript of a toporythmic gene; and (c) is hybridizable to the RNA transcript. The broadest reasonable interpretation of the claims thus still encompasses the treatment of any Notch- or Notch derivative-associated malignancy comprising the use of a genus of protein, antibody or oligonucleotide molecules. For example, the malignancy to be treated in the claims need only express a Notch derivative that is related to a known Notch receptor only in that it can be bound by an antibody that binds a Notch protein, which allows for great breadth considering the varying affinities of antibodies and possible amount of cross-reactivity a given antibody could have. Furthermore, as discussed above, the claimed method encompasses the therapeutic use of a large genus of protein, antibody and oligonucleotide molecules which antagonize the function of a human Notch protein, and for which Applicants have not demonstrated sufficient possession of such a genus of antagonist molecules.

Nature of the Invention

The nature of the invention is complex. Notch and Delta, along with Serrate, are toporythmic proteins known to be involved in cell fate and differentiation, and thus the interaction of these genes and proteins are important in numerous different

developmental roles and functions (see Background of the Invention). The present invention characterizes the binding interaction between Notch protein and Delta protein, demonstrating that EGF repeats 11 and 12 of Notch, which are located in the extracellular domain of Notch, are required and sufficient for Notch-Delta mediated aggregation. Further analysis found that interactions with Delta do not require the intracellular domain of Notch (see section 6.2.5). Similarly, the specification demonstrates that the two EGF repeats of Notch which mediate interactions with Delta, namely EGF repeats 11 and 12, also constitute a Serrate binding domain (see Section 8). The disclosure goes into great detail about the cloning, sequencing, and expression of the human Notch homologs (hN and TAN-1) (see Section 9). Finally, the instant specification demonstrates that human Notch protein expression (measured by immunohistochemical staining using monoclonal antibodies raised against sequences of hN and TAN-1) is increased in at least three patient samples of human cancers: cervical, breast and colon cancer (Section 10.1). The disclosure postulates that "[t]his broad spectrum of different neoplasias in which there is elevated Notch expression suggests that many more cancerous conditions will be seen to upregulate Notch." (p. 85, lines 22-24). Accordingly, the application proposes that disorders of cell fate or differentiation can be treated by administration of a therapeutic compound of the invention, which therapeutics include Notch protein and analogs and derivatives thereof; antibodies thereto; nucleic acids encoding the Notch proteins, analogs or derivatives; Notch antisense nucleic acids; as well as toporythmic proteins and derivatives and analogs thereof (see Section 5 at p. 11).

The Amount of Direction or Guidance Presented and the Presence or Absence of Working Examples

The specification teaches that therapeutics which antagonize, or inhibit, Notch function include Notch antisense nucleic acids, anti-Notch neutralizing antibodies, competitive inhibitors of Notch protein-protein interaction (e.g., a protein comprising Notch EGF-like repeats 11 and 12 (ELR-11, ELR-12)), and molecules which interfere with notch intracellular function such as that mediated by the cdc10 repeats (see paragraph spanning p. 11-12). According to the disclosure, a Notch antisense oligonucleotide preferably comprises a sequence antisense to the sequence encoding ELR 11 and ELR 12 of Notch (p. 32, lines 20-25). An anti-Notch antibody is taught to include antibodies specific to EGF-like repeats 11 and 12 of Notch, or antibodies reactive with the extracellular domain of Notch (which may prevent aggregation in an *in vitro* assay) (see Section 5.11 at p. 56, lines 12-15). With respect to therapeutic protein molecules, the disclosure broadly explains that Notch proteins, derivatives and analogs, as well as Notch fragments and analogs and derivatives of such fragments, other toporythmic (e.g., Delta, Serrate) protein fragments, and analogs or derivatives thereof, as well as inhibitors (e.g., peptide inhibitors) of the foregoing toporythmic protein interactions with Notch, are within the scope of the present invention (see Sections 5.9 – 5.9.2).

With respect to the disease treatment, the specification teaches that therapeutic agents may be screened *in vitro* for their ability to inhibit survival or growth of malignant cells (e.g., by promoting terminal differentiation); such inhibitory agents would be

selected for therapeutic use *in vivo* (p. 15, lines 13-22). However, no such screening assays are actually demonstrated by Applicant, nor are any actual inhibitory or antagonist molecules demonstrated by the disclosure as filed. There are no working examples pertaining to the therapeutic use of any Notch antagonist – such as a protein, antibody, or oligonucleotide as claimed – to antagonize a function of Notch so as to treat a malignancy in human (or any other animal for that matter). Therefore, although the instant specification states that Notch antagonists can be used to treat Notch-related malignancies, there is no actual evidence demonstrating a specific antagonist (or antagonists) or its therapeutic efficacy either *in vitro* or *in vivo*.

The State of the Prior Art

The prior art is relatively sparse with respect to the involvement of Notch or Notch derivatives in malignancies. Jhappan et al. (*Genes Dev.* 1992 Mar; 6(3): 345-355; reference C31 on 01/24/2005 IDS) indicates that expression of a Notch-related int-3 transgene is found in mammary and other glandular epithelia. And Ellisen et al. (*Cell.* 1991; 66:649-661; reference C20 on 01/24/2011 IDS) suggest that chromosomal translocations in the gene TAN-1 may play a role in the pathogenesis of some T cell neoplasms. However, the prior art is completely silent with respect to the use of Notch antagonists for the treatment of human malignancies.

The Relative Skill of Those in the Art and the Predictability or Unpredictability of the Art

While the skill level in the art is high, the level of predictability is quite low. As discussed previously (see office action mailed 08/09/2007), the relevant (post-filing) literature teaches that mammals have four Notch receptor genes (N1-N4), which differ

in the number of EGF-like repeats and length of the intracellular domain (Nickoloff et al. *Oncogene* 2003; 22:6598-6608; p. 6598, column 2, 1st paragraph; and Harper et al. *Clin Genet.* 2003; 64:461-472; p. 461, paragraph 1; both of record). Harper et al. further state that although Notch plays a role in neoplastic cell tansformation, N1 (Notch 1) can also function as a tumor suppressor in the skin of mouse (see p. 467, column 2). However, the art acknowledges that many aspects of Notch signaling are poorly understood, because of the "overlapping versus distinct functions in a given developmental context" (Harper, p. 469). Also unknown, particularly at the time of filing, are the differences in Notch signaling between a normal and a malignant state. The presence of different Notch isoforms in different cancers, their individual effects and the functional relationship between each of the isoforms add to the complexity of the signaling pathways. Notch-induced transformation is further confounded by the fact that different Notch receptors are involved in different stages of tumor progression, and the receptors are shown to function as downstream mediators of each other (Nickoloff, p. 6602). Notably, such pertinent information would not have been available to the skilled artisan at the time the present invention was filed, and thus the artisan would have been constrained to the inadequate teachings of the specification with respect to making a Notch antagonist and using it to treat human malignancies.

Given the limited teachings of present application, the skilled artisan would have reasonably focused on the ligand binding region of Notch, which is the extracellular portion containing ELR-11 and ELR-12, for development of the claimed antagonist protein, antibody or oligonucleotide molecules. The disclosure specifically directs the

skilled artisan to this region of Notch (e.g., a protein comprising Notch ELR-11 and ELR-12 is suggested as a therapeutic molecule) as important for Notch/Delta or Notch/Serrate interaction and as being important for Notch receptor function. However, there is no evidence in the specification as filed that molecules directed to this region would necessarily be inhibitory. On the contrary, post-filing art indicates that molecules directed to the extracellular domain of Notch can act as agonists of Notch receptor function. For example, Conboy et al. (*Science*, 2003; 302:1575-1577) describes the use of an anti-Notch-1 specific antibody, which is directed to the extracellular domain of Notch, as a Notch *activator* (see Fig. 4 on p.1577). Similarly, Li et al. (*J Biol Chem.* 2008; 283(12):8046-8054; reference C103 on 02/11/2008 IDS) report that Notch-3-specific antibodies directed against the EGF repeat region (which would comprise ELR-11 and ELR-12) are either very weak or ineffective in inhibiting various types of ligand-induced Notch-3 signaling (see, in particular, p. 8049). Thus, the art indicates that molecules directed to the extracellular ligand binding domain of Notch do not necessarily function as antagonists, and may in fact activate Notch signaling to stimulate proliferation of cells.

Even when molecules act as antagonists of Notch, it is unclear whether simply antagonizing Notch function would be appropriate for the treatment of hyperproliferative disorders such as cancer. Nickoloff et al. (*Cell Death Differ.* 2002; 9:842-855) demonstrate that a soluble Notch receptor consisting of EGF-like repeats 11 and 12 derived from human Notch1 abolished JAG-1 peptide induced differentiation of human epidermal cells (see p. 851). Similarly, Garces et al. (*J Biol Chem.* 1997;

272(21):29729-29734) show that a recombinant peptide consisting of EGF-like repeats 11 and 12 (Hurn1EGF1112), as well as antisera directed against this peptide, completely inhibited adipocyte differentiation *in vitro* (see p. 29732, 2nd column). Garces also found that Notch antisense prevents hormone-induced adipocyte differentiation. Because cancer and tumor formation is associated with the unrestrained proliferation of undifferentiated cells, it is unclear how inhibiting differentiation in cells (such as by antagonizing Notch) would be beneficial for the treatment of cancer. The use of any Notch antagonist, even those broadly defined by the claims, would therefore be unpredictable in the treatment of human malignancies.

While the dysregulation of Notch signaling has been noted in the post-filing art to be linked with certain cancers, most which originate from epithelial structures, not all malignancies would be amenable to treatment by antagonizing the function of Notch protein. For instance, Wuest et al. (*Arch Dermatol Res.* 2007; 299:493-498) report that increased Notch1 protein expression (as well as Delta1 and Jagged1 (Serrate)) follows treatment with imiquimod (a Toll-like receptor 7 (TLR-7) agonist that activates anti-tumor immune responses) in basal cell carcinoma of the skin (BCC). The authors conclude that imiquimod-mediated *induction* of Notch signaling may exert tumor suppressor function (see abstract). In this instance, therefore, antagonizing Notch function would not be beneficial, and the consequences of antagonizing Notch function for treatment of human malignancies are thus unpredictable.

Moreover, dependent claim 94 lists seminoma as a disease treatable by the instant method. However, there is no evidence that antagonizing Notch will lead to such

treatment. For example, Braydich-Stolle et al. (*Ann NY Acad Sci.* 2005; 1061:94-99) showed that Notch-1 normally induces differentiation in spermatogeonial stem cells. Glial cell line-derived neurotrophic factor (GDNF) increases the expression of the Numb protein, which binds to and causes the endocytosis or ubiquination of the Notch intracellular domain (NICD). GDNF reduces the amount of NICD by promoting production of Numb, thereby blocking Notch-induced differentiation. The authors found that "the overexpression of GDNF in transgenic mice induces aberrant proliferation of spermatogonial stem cells and eventually seminoma-like tumors." This teaches away from antagonizing Notch for seminoma treatment. Based on the findings of Braydich-Stolle et al., one would reasonably expect that antagonism of Notch would lead to reduced differentiation, aberrant proliferation of spermatogonial stem cells and possibly seminoma (see p. 98 "Results and Discussion").

Furthermore, as noted previously (see office action mailed 08/09/2007), at the time of filing, the art was such that the treatment of tumors with antibodies was high unpredictable. For example, Jain (Scientific American, July 1994; of record) describes barriers to the delivery of drugs into solid tumors (for which it is noted that all of the types of cancers recited in claims 91-94 considered solid tumors). These obstacles include (1) non-uniform blood delivery to all areas of the tumor in which some areas of the tumor receive therapeutic agents and other areas of the tumor receive no agent whatsoever (p. 60); (2) increased viscosity of blood in the tumor which hinders drug delivery to the tumor (pp. 60-61); and (3) high liquid pressures in the interstitial matrix that can retard the delivery of large therapeutic agents, such as antibodies, into tumors

(p. 61). While the examiner recognizes that treatment of certain types of cancer using specific antibodies is now recognized as feasible as of today's date (2011), the Jain reference is provided to establish what was known and reasonably expected *at the time of filing* (note also that even the Jain reference is two years post-filing of the earliest effective filing date of the instant application). In other words, at the time of filing, the treatment of cancer using protein therapeutics (as well as nucleic acid based therapies) was unpredictable at best. Given the lack of objective evidence or working examples demonstrating a therapeutic effect for the claimed Notch antagonist molecules, one of skill in the art would not have had a reasonable expectation of success for performing the therapeutic method as claimed. Lack of working examples is given added weight in cases involving an unpredictable and underdeveloped art such as the treatment of cancer with protein (antibody) therapeutics.

The Quantity of Experimentation Necessary

In view the limited guidance of the specification regarding specific Notch inhibitors and absence of working examples directed to the same (particularly in a therapeutic role), the silence of the prior art with respect to the use of Notch antagonists to treat human malignancies, the unpredictability of the post-filing art regarding Notch proteins, antibodies or oligionucleotides to antagonize Notch function consistent with the treatment of a malignancy, the large breadth of the claims which encompasses the use of a broad genus of molecules to treat a genus of human malignancies characterized by an increased expression of Notch and Notch derivatives (which would include proteins as yet unidentified at the time of filing), and the complex nature of the invention, it is the

examiner's determination that undue experimentation would be required of the skilled artisan to practice the claimed invention.

Response to Arguments

11. At pp. 9-10 of the response filed December 21, 2009, Applicants argue that one skilled in the are would not have to engage in undue experimentation in order to practice the claimed invention, and point to the specification and post-filing date evidence that show that a molecule as presently claimed (i.e., as in (i), (ii) or (iii) of claim 34) can disrupt Notch function. Applicants insist that the Examiner has presented no evidence to the contrary.

Applicants' argument has been fully considered but is not persuasive. As noted above, the present specification provides only very limited specific guidance as to Notch antagonists, and does not in fact demonstrate any examples of a Notch antagonist that could be used to treat a malignancy characterized by increased Notch activity or expression as claimed. Rather, the specification discloses a very broad genus of *potential* therapeutic molecules that are described functionally but not structurally, and further states that screening assays could be used to identify appropriate molecules. Therefore, one of skill in the art would have to resort to trial and error experimentation to first identify an appropriate antagonist molecule of Notch and then test its efficacy in cancer models (either *in vitro* or *in vivo*) before being able to treat a human having a disease or disorder that is a malignancy characterized by increased Notch activity or expression. Such additional experimentation is considered undue. Additionally, as discussed above, the examiner has provided relevant post-filing art examples

demonstrating the unpredictability of molecules directed to the extracellular domain of Notch (which is the main region specifically pointed to the by the disclosure as a target for development of therapeutic agents) in their ability to antagonize Notch consistent with a therapeutic role for the treatment of malignancy.

At pp. 10-13 of the response, Applicants present several post-filing references which are alleged to demonstrate the ability of proteins that are capable of inhibiting the interaction of a Notch protein with another toporythmic protein, including antibodies and oligonucleotides, and the usefulness of such molecules in the treatment of malignancy.

Applicant's arguments have been fully considered but are not persuasive. The post-filing art references are not commensurate in scope with the presently claimed invention, nor with what is disclosed in the application as filed. Each of the cited references will be addressed in turn. While Applicant may indeed rely upon post-filing date references to demonstrate the accuracy of a statement made in the specification, such secondary evidence must be commensurate in scope with the claimed invention. As stated in *Rasmusson v. SmithKline Beecham Corp.*, 75 USPQ2d 1297-1303 (CAFC 2005), "If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to 'inventions' consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the 'inventor' would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

In the instant case, the present specification provides general teachings on types of molecules that could be used to antagonize the function of Notch, such as a protein that is capable of inhibiting the interaction of Notch with another toporythmic protein, an antibody to human notch protein, or an oligonucleotide which is at least 6 nucleotides of a sequence complementary to at least a portion of a RNA transcript of a toporythmic gene and is hybridizable thereto. However, the cited art references describe very specific molecules for which the instant application provides no guidance or descriptive support that would direct the skilled artisan to such a molecule. In other words, none of the specific molecules of the post-filing references could have been envisioned by the skilled artisan based upon the teachings of the present disclosure. At the very least, the post-filing art molecules would have required extensive amounts of additional experimentation (and additional knowledge on the functioning of Notch, Notch ligands, and Notch signaling in malignant states as noted above) to arrive at.

For instance, Moellering et al. (*Nature*, 2009; 462(12):182-188; Ref. C121) describe the use of a hydrocarbon-stapled α-helical peptide (SAHM1) derived from a dominant-negative fragment of mastermind-like protein 1 (dnMAML1) to inhibit Notch activation within the intracellular domain of Notch. Importantly, however, the MAML family of proteins, and their interaction with Notch to form a transactivation complex, was not discovered until at least 2000. Therefore the specific structure and/or sequence of such SAHM1 peptides, particularly the hydrocarbon-stapling modification critical to obtaining effective inhibitory activity of these peptides, is not in any supported or described by the instant specification.

Veerarghavalu et al. (*J Virology*, 2004; 78:8687-8700; Ref. C93), Purow et al. (*Cancer Res.* 2005; 65(6):2353-2363; Ref. C88), and Park et al. (Cancer Res. 2006; 66: 6312-6318; Ref. C105) each teach the use of siRNA molecules for antagonizing Notch function. Small interference RNA (siRNA) technology, however, was not known until at least 1998, and it potential for therapeutic use was not readily recognized in the art until at least a decade after the earliest claimed filing date of the present application. Additionally, the peptide used by Veeraghavalu (Jagged-1 fragment) is not commensurate in scope with the broadly claimed inhibitory protein of claim 34, nor is the specific sequence of the Veeraghavaly peptide (or even the relative region of the Serrate homolog) described by the present application. Therefore, there would have been no means by which the skilled artisan could have identified or designed such molecules based only upon the guidance of the specification and knowledge in the prior art.

Kiaris et al. (2004; Ref. C81) reports that the expression of Deltex, a gene noted by the authors to modulate the Notch signaling pathway, in transgenic mouse mammary tumor model which express the intracellular domain of Notch ($N1^{IC}$) could inhibit Hras1-drivevn, cyclin D1-dependent mammary oncogenesis. Here, no protein, antibody or oligonucleotide was administered therapeutically. The method by Kiaris would effectively equate gene therapy, which is beyond the scope of the presently claimed invention. Moreover, it is noted that the Deltex gene, its structure, and interaction with Notch was unknown at the time of filing, and thus would not have been available to the skilled artisan for thus in the present method.

Wu et al. (2010; Ref. C124) and Li et al. (2008; Ref. C103) each describe the use of anti-Notch antibodies. However, in each instance, the antibodies were highly selected through rigorous screening techniques based on knowledge of binding properties and functional interactions unknown at the time of filing. For instance, both Wu et al. and Li et al. teach anti-Notch antibodies directed to the negative regulatory region (NRR) of Notch as being effective for antagonizing Notch activity consistent with a therapeutic role. Yet this NRR region is not disclosed in the present application as a target for antagonism of Notch, nor is there any support or guidance that would direct the skilled artisan to produce antibodies against this specific intracellular region of Notch.

Krop et al. (2006; Ref. C107), Kogoshi et al. (2007; Ref. C104), Park et al. (as above), Konishi et al. (2007; Ref. C106), and both Farnie et al. references (Refs. C108 and C109) each teach the use of γ-secretase inhibitors to suppress Notch activation/function. However, the role of γ-secretase in the processing of Notch was not known or well-established in the art at the time of filing, nor was the use of γ-secretase inhibitors for treatment of disease. Furthermore, no guidance or description of such inhibitors is contemplated by the instant specification.

Additionally, the Farnie I and Farnie II references and the Dontu et al. (2004; Ref. C110) each teach the use of a Notch 4 antibody. However, the present specification provides no disclosure on the sequence for the Notch 4 protein or its involvement in malignancy. In fact, the instant application does not even recognize the existence of Notch 4; only the human Notch1 protein sequence is disclosed. Therefore, the skilled

artisan would not have been able to make or even identify a neutralizing anti-Notch 4 antibody using only the guidance of the present invention. In other words, an anti-Notch 4 antibody is not commensurate in scope with what is disclosed in the present invention.

At p. 13 of the response, Applicants again point to the Reedijk, Büchler, Nam, Jundt, Miele, Jang, Hoek, Hayashi, Dang, Patel, Santagat, and Harper references (of record), which allegedly show that activated Notch function is associated with malignancy, and suggest that antagonizing Notch can be therapeutically useful for treatment of malignancies. Therefore, Applicants argue at p. 14 that the foregoing evidence is sufficient to convince one skilled in the art of Applicants' asserted utility, i.e., that the antagonists of Notch function can be used to treat a malignancy.

Applicants' argument has been considered but is not found persuasive. The examiner agrees that one skilled in the art would find the present invention useful. The asserted utility as it applies under 35 U.S.C. 101 is not contested here, but rather the enablement of the present invention is lacking. The instant application's generic and broad disclosure of antagonist molecules and absence of any actual examples or demonstrated uses of such antagonists does not provide sufficient guidance to enable one of skill in the art to practice the therapeutic method as claimed. While the post-filing art references clearly show that increased Notch expression is involved in certain types of cancer and that inhibition of Notch activity in these cancer models is associated with beneficial outcomes, there is nothing in the present specification that would have guided the skilled artisan to these specific antagonist molecules. In other words, the antagonist molecules of the post-filing references are not commensurate in scope with the

presently claimed invention. If anything, the post-filing references as a whole serve to illustrate the complex nature of the invention, and also how much additional knowledge, experimentation, and consideration would have been required of the skilled artisan beyond what is provided in the present disclosure in order to develop appropriate antagonist molecules.

Finally at pp. 14-15 of the response, Applicants assert that in view of the evidence presented, it would not be undue experimentation to determine which molecule of the Notch pathway could be antagonized since the data leads the skilled artisan to reasonably predict that antagonizing any molecule of the Notch pathway will antagonized Notch function and provide predictable therapeutic results in the treatment of malignancies.

Applicants' argument has been considered but is not persuasive. While the post-filing art may demonstrate that inhibition of the Notch signaling pathway at the point of (i) Notch-ligand binding, (ii) Notch receptor processing, and (iii) Notch transcriptional complex formation may each be useful, again it is emphasized that much of this Notch signaling pathway, including particular Notch ligands, γ-secretase processing of Notch, or transcription complex formation, was not known at the time of filing nor is provided in the present specification as filed. Much of the technology used to establish these molecular signaling pathways and to identify the Notch antagonists of the post-filing references (such as siRNA) was not even available to the skilled artisan at the time of filing of the present invention. Moreover, evidence has been presented above indicating that even if the skilled artisan were to follow what limited guidance is provided in the

disclosure, it is unpredictable that such molecules would function as intended by the claims (i.e., they may either be Notch agonists or may enhance proliferation of malignant cells). Therefore, it cannot be said that claimed subject matter is predictable, nor that sufficient guidance has been provided in the present disclosure to correct for such unpredictability. Accordingly, the claimed invention lacks enablement under 35 U.S.C. 112, first paragraph.

Claim Rejections - 35 USC § 112, second paragraph

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 34, 91-94 and 115 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 34 recites an oligonucleotide which "consists of at least six nucleotides" and "consists of at least a sequence complementary to at least a portion of a RNA transcript..." The transitional phrase "consists of" or "consisting of" excludes any element, step, or ingredient not specified in the claim, that is, it is considered "closed" claim language. See MPEP 2111.03. However, this phrase is then followed by the phrase "at least", which is open-ended. Thus, "consists of at least six nucleotides" is ambiguous and indefinite because it is unclear whether the oligonucleotide is limited to 6 nucleotides total or whether longer sequences are encompassed by the claim. Similarly, the phrase "consists of at least a sequence complementary to at least a

portion of a RNA transcript..." is ambiguous because it is unclear whether the oligonucleotide is limited to a specific sequence or whether it may contain other elements (besides a complementary nucleic acid sequence). The metes and bounds of the claimed oligonucleotide thus cannot be readily determined. Dependent claims 91-94 and 115 are included in this rejection because they include all of the limitations of base claim 34, yet contain nothing in addition that would rectify the noted deficiency.

Double Patenting

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 34, 91-94 and 115 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 99, 106 and 107 of copending Application No. 11/546,583. Although the conflicting claims are not identical, they are not patentably distinct from each other because in each case the claims encompass treatment of a subject having a disease or disorder that is a malignancy characterized by increased Notch activity or increased expression of a Notch protein comprising administering a protein which is able to antagonize Notch function. Both the instant claims and the claims of the '583 application also recite that he disease or disorder is cervical cancer, breast cancer, colon cancer, melanoma, or lung cancer. Therefore, the claims of the '583 application render obvious the presently claimed invention.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

16. No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Ballard whose telephone number is (571)272-2150. The examiner can normally be reached on Monday-Friday 8:30 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ali Salimi can be reached on 571-272-0909. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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